that the '338 patent is at least partially inoperative. Specifically, the Patent Owner believes that the inventors claimed, without any deceptive intent, less than they had the right to claim because the '338 patent does not contain claims of intermediate scope. These new intermediate scope claims provide additional protection for several narrower aspects of the invention. Thus, the Patent Owner seeks to add new claims 41-59 to obtain that protection.

Finally, a licensee of the '338 patent has suggested that the claims of the '338 patent might be read so broadly as to encompass prior art from an earlier period of molecular biology. The recitation in these new claims of three specific narrower aspects of the invention demonstrates more clearly that the claimed invention does not encompass this early art and, in any event, explicitly and even more clearly excludes the cited art. *See* Hewlett-Packard Co. v. Bausch & Lomb, Inc., 882 F.2d 1556, 1564-1565, 11 U.S.P.Q.2d 1750, 1757 (Fed. Cir. 1989) (expressing tacit approval of filing narrower claims in reissue, citing *In re Handel* 312 F.2d 943, 945- 46 n.2, 136 U.S.P.Q. 460, 462 n.2 (C.C.P.A. 1963)).

Thus, the Patent Owner respectfully requests entry of these amendments. With the requested amendments, claims 1-59 will be pending.

A. The Invention

As set forth during prosecution, the invention of the '338 patent provides polynucleotide assays that combine "target purification methods with target amplification methods." Paper No. 8, Preliminary Amendment of Dec. 5, 1995, at p. 11-12; Paper No. 12, Amendment of Oct. 24, 1996, at p. 10. Based on this combination, the invention provides methods of amplification that produce large amounts of purified target polynucleotide as well as methods of detection that

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yield assays of great sensitivity. *Id.* Thus, the '338 patent issued with claims to methods of amplifying a target polynucleotide, methods of detecting a target polynucleotide, as well as kits for both amplifying and detecting.

Each of the claims, whether to amplification methods, detection methods, or kits, shares the sequential elements of purifying or separating the target polynucleotide from the sample and then amplifying the target polynucleotide. This particular combination of steps would not have been apparent or desirable to those in the nucleic acid assay art in December 1987, as set forth by the declaration of Dr. David Persing submitted during the prosecution of the '338 case.[1] Viewing it from the standpoint of amplification, those in the art believed that PCR (one of the primary methods of nucleic acid amplification) was so highly specific, based as it was on the careful selection of primers, that there was no need to isolate or separate target polynucleotides. Paper No. 20, Persing Declaration, ¶ 12. And, according to Dr. Persing, it was not until after December 1987 that those in the art recognized that careful selection of primers was not enough to avoid non-specific amplification. *Id.*

Second, from the binding/separating standpoint, it was generally understood that binding of the target to a probe/support was "substantially less than 100%." Thus, for assays in which the level of target polynucleotide was low, the use of a binding/separating step would decrease the already low amount of target available for detecting. Added to these concerns was the general

[1] A draft declaration was submitted on July 11, 1997 (Paper No. 20), and notice of the submission of the executed version was filed on July 11, 1997 (Paper No. 21).

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desire to avoid the addition of complex steps to the assay. Paper No. 20, Persing Declaration, ¶ 13. Accordingly, Dr. Persing concluded that:

> [C]oupled with the conventional understanding at that time (that careful selection of primers would permit adequate selectivity of target and specificity in the amplification product), the practitioners' concern regarding imperfect binding efficiencies and the expected loss of real target before amplification occurred reinforced their incentive to avoid further complicating their assays by the addition of target separation steps to their assays.

Paper No. 20, Persing Declaration, ¶ 13.[2]

The Examiner agreed in the Notice of Allowance, stating that:

> [T]he art at the time of filing did not recognize that the efficiency of PCR amplification would decrease due to the presence of contaminants in a sample and therefore provided no motivation to purify a target sample from a heterogenous sample of nucleic acids prior to amplification. Having not recognized the problem, applicant's solution therefore, while utilizing routine methodology to modify PCR amplification techniques, would not have been obvious at the time that the invention was made. The Declaration of Dr. David Pershing [sic] further supports this conclusion as providing further evidence concerning the skill of the art at the time of filing, attesting that one of skill in the art would likely stay away from combining a hybridization capture method with a PCR method since one would not be motivated to provide a method with the potential to lose target nucleic acids prior to amplification.

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2 Dr. Persing also noted an advantage of the claimed method that was unexpected in or before December 1987. Specifically, separating the target prior to amplification eliminates the effect of amplification inhibitors that are normally present in the sample system, thereby permitting amplification to proceed optimally. Paper No. 20, Persing Declaration, ¶ 14.

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Paper No. 23, Notice of Allowability, p. 3.[3]

Thus, claims 1-40 issued. As noted above, the claims recite methods of amplification (independent claims 1, 27, and 34), methods of detection (independent claims 7, 19, 28, and 38), and kits (independent claims 20 and 24). The claims provide for a variety of methods for separating the target polynucleotide, the simplest being providing a support to which the target polynucleotide binds and then removing the support from the sample (claims 1 and 7). Alternatively, the claims specify separation of the target by providing a probe which binds to the target and then providing a support which binds to the probe (claims 27 and 28) or by providing a support and a probe which binds to the target and to the support (claim 34 and 38). Similarly, the claims provide for a variety of methods for amplifying the separated target polynucleotide. The target polynucleotide can be amplified with any polymerase (claims 4, 10, 17, 25, 29, 35 and 39) or with a DNA polymerase, an RNA polymerase, a transcriptase, or Qβ replicase (claims 5, 11, 30, and 36).

[3] The Notice of Allowability speaks in reference to PCR in explaining the reasons for allowance. The inclusion of dependent claims that involve enzymes that were not and are not used in PCR (pending dependent claims 29 and 35 (which issued as claims 5 and 11, respectively) recite RNA polymerase and Qβ replicase) demonstrates, however, that the claims were never limited just to PCR, although they clearly were *in vitro* methods and were intended to be limited to making many copies of the target nucleic acid molecules as in PCR.

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B. Claims of Intermediate Scope

Despite these specifically claimed elements of the amplification process, the specification discloses other aspects of the amplification method that had not been claimed. Accordingly, the Patent Owner seeks in this reissue application to add these aspects of the amplification process as claims of intermediate scope to provide additional protection to the claimed invention.

Specifically, the Patent Owner has added claims 41, 47, and 53-59 (which depend directly from each of the originally issued independent method of amplification claims 1, 27, and 34, from the method of detection claims 7, 19, 28 and 38, and from the kit claims 20 and 24)[4] that narrow the amplification method in three specific aspects. First, these new claims recite that the

[4] To orient the Office, the Patent Owner provides the following chart of the added claims and their relationship to the issued claims:

Type of claim	Original claim	Added claims
Method of amplification	1	41-46
	27	56
	34	58
Method of detection	7	47-52
	19	53
	28	57
	38	59
Kits	20	54
	24	55

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amplification process is conducted *in vitro*. Each of the amplification examples set forth in the specification describes an *in vitro* method, as follows:

> - Example 4 describes amplification via *E. coli* RNA polymerase that lacks the sigma subunit (i.e., core RNA polymerase) together with nucleotide triphosphates and a low salt transcription buffer. See col. 30, line 59 to col. 31, line 19.
>
> - Example 5 sets forth a two stage process of amplification, first using DNA polymerase, random oligohexamer primers, and deoxynucleotide triphosphates in buffer to replicate the DNA and to produce additional double stranded DNA, followed by the addition of core RNA polymerase, nucleotide triphosphates and a low salt transcription buffer to form many RNA copies of the DNA. See col. 31, lines 28-54.
>
> - Example 6 amplifies first by non-specific double stranded DNA synthesis, as set forth in the first part of Example 5, followed by cycles of heating to form single stranded DNA and then polymerizing with additional DNA polymerase to yield an approximately 1,000 fold increase in the level of DNA. See col. 31, line 60 to col. 32, line 5.
>
> - Example 7 describes the exponential replication of RNA with Qβ replicase. See col. 32, lines 10-19.

Thus, these Examples support *in vitro* amplification methods.

Second, the intermediate claims all recite the production of a "multitude of amplification products." Express literal support is set forth in the specification, which states that:

> In Step 3 of FIGS 4, 5, and 6, the isolated target is non-specifically amplified to form a **multitude of amplification products**.

See col. 15, lines 56-58. In addition, because each of Figures 4, 5, and 6 corresponds to Examples 4, 5, and 6, respectively, these examples and figures support this limitation. Finally,

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Example 7 supports the formation of a multitude of amplification products by its recitation of "exponential" replication of RNA.

Third, the intermediate claims also specify that the amplification products produced are "polynucleotide amplification products." That limitation finds support in the definition of "amplification" which recites enzymes that can only produce polynucleotide amplification products from polynucleotide targets, as follows:

> In the situation where the target is a polynucleotide, additional target, or target-like molecules, or molecules subject to detecting can be made enzymatically with DNA or RNA polymerases or transcriptases.

See col. 2, lines 16-19. In addition, all of the amplification examples (Examples 4-7) result in the production of polynucleotide amplification products, i.e., either RNA or DNA.

In addition to these intermediate claims, the Patent Owner has included additional dependent claims to the claims that ultimately depend from claims 1 and 7 to specify additional aspects of the amplification method. Specifically, claims 42, 45, 48, and 51 claim amplification wherein the amplification is linear or exponential. Examples 4 and 5, with their one-at-a time transcription of RNA and/or replication of DNA, are linear, while Examples 6 and 7, with the doubling of DNA per cycle, provide for exponential amplification. Indeed, Example 7 expressly notes the exponential nature of the process at col. 32, lines 17-19. Further dependent claims 43 and 49 specify an exponential amplification process.

The Patent Owner has also added dependent claims 44 and 50 to recite the use of a polymerase and at least one oligonucleotide primer because the specification covers

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amplification both with and without primers. The support for claims with primers is expressly set forth in Examples 5-6, while the support for amplification without primers is set forth in Example 4.

Finally, the specification describes amplification methods based on more than one polymerase (see Example 5), and claims 46 and 52 cover those embodiments.

C. The Cited Art

As noted above, the lack of these intermediate claims has apparently resulted in some confusion regarding the scope of protection afforded by the patent because a licensee of the '338 patent has identified art that the licensee believes renders the claims unpatentable.[5] That licensee has suggested that the term "amplify" is used so broadly in the specification that the amplification method[6] includes the cloning of polynucleotides by growth in transformed cells; the production of cell-free translation products; and the enzymatic reproduction of a

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5 See redacted letter from licensee, attached at Tab 1.

6 Although the licensee did not identify the particular claims to which these references applied, the licensee's characterization of the art demonstrates that the only claims to which the references could apply are the method of amplification claim 1 and the method of detection claim 7 and arguably to claims 34 and 38. Specifically, the licensee has urged that the references provide the binding of polynucleotides to solid supports, separating the support and the bound polynucleotide from the sample, and subsequently amplifying the polynucleotide. As noted above, both of these claims 1 and 7 recite the simplest capture method: contacting the sample with a first support, separating the support and bound target from the sample. Other independent claims recite additional elements. Specifically, the method of detecting claim 19 recites the step of separating out amplified target with a second support prior to detecting. The method of amplification claim 27 and the corresponding method of detection claim 28 further recite providing a probe which binds the target polynucleotide. Moreover, the references provide no suggestion for kits for amplification or detection as in claims 20 or 24.

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polynucleotide. The publications cited by the licensee and another publication that appears to be of the same ilk are submitted in an accompanying Information Disclosure Statement.

This apparent confusion over the protection afforded by the patent does not arise with respect to the intermediate scope claims set forth in this Preliminary Amendment. As noted above, these intermediate scope claims define the amplification element of each of the independent method claims in three separate aspects and thereby more clearly define the amplification method of the invention.

As to the specific differences between the claimed invention and the references set forth in the accompanying IDS, three of the references describe DNA cloning by insertion into a cloning vector and transformation of bacteria. Specifically, Arsenyan et al. *Gene* (1980) describes the insertion of double-stranded DNA, made by annealing purified single-stranded DNA fragments, into pBR325 and the transformation of *E. coli* (see page 101 or 106) and Georgiev et al. *Science* (1977) discusses the substitution of the DNA fragment of interest for the C fragment of the bacteriophage, λgt-λC, and the transfection of *E. coli* (see page 394). Neither of these *in vivo* DNA cloning papers from the earlier period of molecular biology describe the *in vitro* amplification of the claimed methods.

The third reference, Augenlicht, U.S. Patent No. 4,981,783, sets forth the insertion of DNA fragments into pBR322 and the transformation of *E. coli* (col. 5, lines 50-65). The patent also discloses that the number of plasmids per transformed cell is "amplified" by growth in the presence of chloramphenicol. As above, this disclosure of *in vivo* DNA cloning and increasing

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plasmid number has nothing to do with the *in vitro* amplification method of the claimed invention.

Two of the references describe the enzymatic "reproduction" of a particular polynucleotide. Both of these references, Montgomery et al. *P.N.A.S.* (1982) and Boss et al. *P.N.A.S.* (1981), disclose the dideoxynucleotide chain termination technique of Sanger et al. using reverse transcriptase which is, in fact, a sequencing technique. The reverse transcriptase does produce a polynucleotide fragment (i.e., DNA) based on the target sequence but that fragment is not likely to be a copy of the target because the purpose of the sequencing method is to create fragments of different lengths, each ending with a labeled and chain-terminating nucleotide.[7] Moreover, reverse transcriptase can produce only one copy (whether it be a short or long fragment) of the target because it destroys the RNA target as DNA synthesis progresses.[8] Thus, neither of these disclosures sets forth a method that produces a "multitude" of amplification products.

The remaining two references describe cell-free translation methods which produce proteins. Specifically, both Hirsch et al. *P.N.A.S.* (1978) and Strair et al. *P.N.A.S.* (1977) used the "wheat germ cell-free system" to produce protein encoded by the isolated RNA. *See* Hirsch

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[7] *See* Coulsen, A.R., and Staden, R., (1994) "DNA Sequencing" in *The Encyclopedia of Molecular Biology* (Edited by J. Kendrew, E. Lawrence et al., Blackwell Science Ltd, Oxford) pp. 283, 283-284 (copy enclosed).

[8] *See* Coffin, J.M. (1996), "Retroviridae: Viruses and Their Replication" in *Fundamental Virology,* Third Edition (B.N. Field, D.M. Knipe, P.M. Howley et al., eds, Lippincott-Raven Publishers, Philadelphia), pp. 763, 776-778 (copy enclosed).

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at page 1736, right column, third paragraph; Strair at page 4348, right column, third paragraph. This production of protein is clearly outside the production of "polynucleotide amplification products" and, consequently, neither of these references teach the amplification process of the claimed invention.

Finally, the Patent Owner notes that, for substantially analogous reasons, these references do not disclose the invention of the originally presented claims, as properly construed in light of the prosecution history. *See* note 3, *supra*, and associated art.

D. Conclusion

For the foregoing reasons, the Patent Owner respectfully submits that claims 1-59 are in condition for allowance and earnestly requests early notification to this effect.

If there are any fees due in connection with the filing of this Preliminary Amendment not already accounted for, please charge the fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: March 8, 2000

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